Original Investigation

Risk of Cerebral Venous Thrombosis in Obese Women

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IMPORTANCE Obesity is a risk factor for deep vein thrombosis of the leg and pulmonary embolism. To date, however, whether obesity is associated with adult cerebral venous thrombosis (CVT) has not been assessed.

OBJECTIVE To assess whether obesity is a risk factor for CVT.

DESIGN, SETTING, AND PARTICIPANTS A case-control study was performed in consecutive adult patients with CVT admitted from July 1, 2006 (Amsterdam), and October 1, 2009 (Berne), through December 31, 2014, to the Academic Medical Center in Amsterdam, the Netherlands, or Inselspital University Hospital in Berne, Switzerland. The control group was composed of individuals from the control population of the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis study, which was a large Dutch case-control study performed from March 1, 1999, to September 31, 2004, and in which risk factors for deep vein thrombosis and pulmonary embolism were assessed. Data analysis was performed from January 2 to July 12, 2015.

MAIN OUTCOMES AND MEASURES Obesity was determined by body mass index (BMI). A BMI of 30 or greater was considered to indicate obesity, and a BMI of 25 to 29.99 was considered to indicate overweight. A multiple imputation procedure was used for missing data. We adjusted for sex, age, history of cancer, ethnicity, smoking status, and oral contraceptive use. Individuals with normal weight (BMI <25) were the reference category.

RESULTS The study included 186 cases and 6134 controls. Cases were younger (median age, 40 vs 48 years), more often female (133 [71.5%] vs 3220 [52.5%]), more often used oral contraceptives (97 [72.9%] vs 758 [23.5%] of women), and more frequently had a history of cancer (17 [9.1%] vs 235 [3.8%]) compared with controls. Obesity (BMI ≥30) was associated with an increased risk of CVT (adjusted odds ratio [OR], 2.63; 95% CI, 1.53-4.54). Stratification by sex revealed a strong association between CVT and obesity in women (adjusted OR, 3.50; 95% CI, 2.00-6.14) but not in men (adjusted OR, 1.16; 95% CI, 0.25-5.30). Further stratification revealed that, in women who used oral contraceptives, overweight and obesity were associated with an increased risk of CVT in a dose-dependent manner (BMI 25.0-29.9: adjusted OR, 11.87; 95% CI, 5.94-23.74; BMI ≥30: adjusted OR, 29.26; 95% CI, 13.47-63.60). No association was found in women who did not use oral contraceptives.

CONCLUSIONS AND RELEVANCE Obesity is a strong risk factor for CVT in women who use oral contraceptives.

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Various studies[1-6] have identified obesity as a risk factor for deep vein thrombosis of the leg and pulmonary embolism, collectively called venous thromboembolism (VTE). A body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) of 30 or more increases the risk of VTE approximately 2-fold compared with a normal BMI (<25), and this risk increases more with higher BMIs. Individuals with a BMI greater than 40 have an approximately 3 times higher risk.

Cerebral venous thrombosis (CVT) is a rare thrombotic condition that mainly affects young adults and children.[7] Risk factors for CVT partly overlap with those for VTE and include thrombophilia, cancer, and oral contraceptive use.[8,9] Other risk factors, such as local infections and head trauma, are specific for CVT.[10] Some diseases, such as acute lymphoblastic leukemia, are associated with CVT and VTE, but the association is stronger for CVT.[11]

To our knowledge, whether obesity is associated with adult CVT has not been assessed. One study[12] found that obesity is more common in children with CVT (55%) compared with controls (32%), but the sample size was small (22 cases). In addition, this study[12] used historical controls and did not adjust for confounding variables. Moreover, because the clinical presentation and risk factors of CVT are different for children and adults,[13] this result cannot be generalized to adult patients. In the current study, we examined whether obesity is a risk factor for adult CVT.

Key Points

Question: Is obesity a risk factor for cerebral venous thrombosis?

Findings: In this case-control study that included 186 cases and 6134 controls, obesity was associated with a statistically significant 3-fold increased risk of cerebral venous thrombosis. Stratification by sex revealed that in women who used oral contraceptives, the risk was increased 30-fold. In contrast, we found no association in men or women who did not use oral contraceptives.

Meaning: Obesity is a strong risk factor for cerebral venous thrombosis in women who use oral contraceptives.

Methods

Study Design and Patient Selection

We performed an unmatched case-control study. The controls were recruited from March 1, 1999, through September 31, 2004, and the cases were recruited from July 1, 2006 (Amsterdam), and October 1, 2009 (Berne), through December 31, 2014. Data analysis was performed from January 2 to July 12, 2015.

Cases were patients with CVT included in 2 prospective cohorts from the Academic Medical Center in Amsterdam, the Netherlands, and Inselspital University Hospital in Berne, Switzerland. In these hospitals, data on consecutive adult patients with CVT have been recorded since July 2006 (Amsterdam) and October 2009 (Berne). We included patients who were admitted until December 2014. The diagnosis of CVT was confirmed with computed tomography venography, magnetic resonance imaging and magnetic resonance venography, angiography, or autopsy in all patients in accordance with international guidelines.[14]

Controls were healthy individuals who participated in the Dutch Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) study.[15] The MEGA study is a case-control study performed in the Netherlands that included 4956 consecutive patients aged 18 to 70 years with a first deep vein thrombosis of the leg or pulmonary embolism from March 1, 1999, through September 31, 2004. Details of this study have been reported.[15] Partners of patients and individuals identified by random digit dialing were asked to participate as controls. In total, 6297 controls (3297 partners and 3000 identified by random digit dialing) were included. These participants were between the ages of 18 and 70 years and had no history of venous thrombosis. We excluded women (cases and controls) who were pregnant or had given birth less than 12 weeks earlier.

The Medical Ethics Committee Academic Medical Center, Committee Medical Ethics Leiden University Medical Centre, and Cantonal Ethics Commission Bern approved the study. Written informed consent was obtained from all participants included in the MEGA study and the Berne cohort. For the patients with CVT included in the Amsterdam cohort, written informed consent was not required under Dutch law because only observational data were collected.

Data Collection and Definition of Obesity

Baseline characteristics, risk factors for thrombosis, imaging findings, and clinical outcome were recorded using a standardized case report form for cases. Each control completed a detailed questionnaire on acquired risk factors for thrombosis, which included self-reported current height and weight. In accordance with the definitions of the World Health Organization, BMI was categorized as follows: normal weight, BMI less than 25; overweight, BMI of 25 to 29.99; and obesity, BMI of 30 or greater.

Statistical Analysis

A multiple imputation procedure was used for missing data on height, weight, oral contraceptive use, smoking status, history of cancer, and ethnicity.[16] In total, 5 data sets were imputed, and results were pooled according to Rubin's rules. We applied multivariate logistic regression analysis to study the association between obesity and CVT. Individuals with a normal BMI (<25) were the reference category. In a separate analysis, we included BMI as a continuous variable in the model. Unadjusted and adjusted odds ratios (ORs) with 95% CIs were calculated. We adjusted for the following prespecified variables: sex, age (as a continuous variable), history of cancer, ethnicity, smoking status, and oral contraceptive use. On the basis of a previous report,[4] we performed predefined subgroup analyses in which we studied the influence of sex and oral contraceptive use on the association between obesity and CVT. $P < .05$ was considered statistically significant. All data were analyzed with SPSS statistical software, version 20 (SPSS Inc).

Table 1. Baseline Characteristics[a]

Characteristic	Cases (n = 186)	Controls (n = 6134)
Age, median (IQR), y	40 (28-49)	48 (38-57)
Female sex	133/186 (71.5)	3220/6134 (52.5)
Oral contraceptive use[b]	97/133 (72.9)	758/3220 (23.5)
History of cancer	17/186 (9.1)	235/6134 (3.8)
White ethnicity	167/186 (89.8)	5805/6134 (94.6)
Current smoker	36/186 (19.4)	1980/6134 (32.3)

Abbreviation: IQR, interquartile range.

[a] Data are presented as number/total number (percentage) of study participants unless otherwise indicated. The number of events was divided by the total number (unknown and missing cases excluded) to calculate the percentage.

[b] In women only.

Table 2. Baseline Characteristics of Cerebral Venous Thrombosis Cases

Characteristic	No./Total No. (%) of Cases (n = 186)[a]
Headache	163/182 (89.6)
Focal neurologic deficits	115/182 (63.2)
Seizures	79/184 (52.0)
Papilledema	38/148 (25.7)
Hemorrhagic infarcts or intracerebral hemorrhage	76/182 (41.8)
Cerebral edema or infarction without hemorrhage	39/182 (21.4)

[a] The number of cases was divided by the total number (unknown and missing cases excluded) to calculate the percentage.

Results

There were 192 cases and 6297 controls within the specified period. We excluded 6 cases and 163 controls because of pregnancy or recent delivery; therefore, the study population consisted of 186 cases and 6134 controls. The numbers of patients for whom data were missing were as follows: height, 547 (64 cases and 483 controls); weight, 539 (57 cases and 482 controls); oral contraceptive use, 32 (6 cases and 26 controls); history of cancer, 20 (1 case and 19 controls); smoking status, 487 (57 cases and 430 controls); and ethnicity, 423 (38 cases and 385 controls). In total, BMI could not be calculated without imputation in 69 cases because height or weight was not available. Eleven of these cases (15.9%) had obesity listed in their medical history.

Cases were younger (median age, 40 vs 48 years), more often female (133 [71.5%] vs 3220 [52.5%]), more often used oral contraceptives (97 [72.9%] vs 758 [23.5%] women), and more frequently had a history of cancer (17 [9.1%] vs 235 [3.8%]) compared with controls (**Table 1**). The most common clinical manifestations of patients with CVT are provided in **Table 2**.

Mean BMI was higher in cases than controls (26.7 vs 25.6, $P = .01$). After adjustment for confounding variables, the risk of CVT was increased in patients with obesity (BMI ≥30; adjusted OR, 2.63; 95% CI, 1.53-4.54) compared with patients with a normal BMI (**Table 3**). Overweight (BMI 25.0-29.99) was not associated with CVT (adjusted OR, 1.37; 95% CI, 0.80-2.36). When included as a continuous variable, BMI was also associated with an increased risk of CVT (adjusted OR per 1-unit increase in BMI, 1.09; 95% CI, 1.05-1.13; $P < .001$).

Stratification by sex revealed no statistically significant association between obesity and the risk of CVT in men (adjusted OR, 1.16; 95% CI, 0.25-5.30; **Table 4**). In women, overweight and obesity were associated with CVT (BMI 25-29.9: adjusted OR, 1.71; 95% CI, 1.01-2.91; BMI ≥30: adjusted OR, 3.50; 95% CI, 2.00-6.14).

We also stratified for oral contraceptive use (**Table 5**). Among women who did not use oral contraceptives, we found no association between obesity and CVT (BMI ≥30: adjusted OR, 1.29; 95% CI, 0.46-3.66). In contrast, in women who used oral contraceptives, obesity was strongly associated with the risk of CVT. Compared with women with a normal weight who did not use oral contraceptives, obese women taking oral contraceptives had a 29-fold increased risk of CVT (adjusted OR, 29.26; 95% CI, 13.47-63.60). The risk of CVT was also increased in overweight women who used oral contraceptives (BMI 25-29.99: adjusted OR, 11.87; 95% CI, 5.94-23.74).

Discussion

Our study indicates that obesity (BMI ≥30) is associated with an increased risk of CVT. This association appears to be fully attributable to a strongly increased risk in women who use oral contraceptives. Among these women, obesity was associated with an almost 30-fold increased risk of CVT compared with women of normal weight who did not use oral contraceptives. In men and women who do not use oral contraceptives, we found no association between CVT and obesity.

In VTE, the association with obesity is also stronger in women than men. In a large cohort study,[5] a BMI in the highest quartile increased the risk of VTE 2.8-fold for women and 1.7-fold for men. Another study[3] confirmed similar effect sizes. Only a few studies[4,17,18] have examined the interaction between oral contraceptive use and obesity on the risk of VTE. Pomp et al[4] found an OR of 24 among women with a BMI of 30 or greater who used oral contraceptives compared with nonusers of oral contraceptives who were of normal weight. In another study,[17] the risk of VTE in oral contraceptive users with a BMI of 30 or greater was increased approximately 10-fold. A possible interaction between oral contraceptives and obesity has also been observed in ischemic stroke. In a case-control study by Kemmeren et al,[18] the risk of ischemic stroke in women who used oral contraceptives was approximately doubled in those with obesity.

Among oral contraceptive users, the risk of CVT was higher in those with obesity (BMI ≥30) than in women who were overweight (BMI 25-29.99). This dose-response effect, in combination with the magnitude of the effect size and the evidence that obesity is also associated with VTE,[2,4,19] favors a causal association among obesity, oral contraceptive use, and CVT.[20] One mechanism by which obesity could increase the risk of thrombosis are changes in coagulation factor levels. Compared with women with a normal weight, obese

Table 3. Association Between Obesity and Cerebral Venous Thrombosis

BMI	No. (%) of Study Participants[a]		OR (95% CI)	
	Cases (n = 186)	Controls (n = 6134)	Unadjusted	Adjusted[b]
<25	85 (45.7)	3025 (49.3)	1 [Reference]	1 [Reference]
25-29.99	59 (31.7)	2299 (37.5)	0.93 (0.57-1.50)	1.37 (0.80-2.36)
≥30	42 (22.6)	810 (13.2)	1.85 (1.14-3.00)	2.63 (1.53-4.54)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio.

[a] The number of study participants was divided by the total number (unknown and missing cases excluded) to calculate the percentage.

[b] The multivariate model is adjusted for sex, age, history of cancer, ethnicity, smoking status, and oral contraceptive use.

Table 4. Stratification by Sex

BMI	No. (%) of Study Participants[a]		OR (95% CI)	
	Cases (n = 53 Men and 133 Women)	Controls (n = 2914 Men and 3220 Women)	Unadjusted	Adjusted[b]
Men				
<25	27 (50.9)	1277 (43.8)	1 [Reference][c]	1 [Reference][c]
25-29.99	18 (34.0)	1270 (43.6)	0.66 (0.30-1.45)	0.80 (0.35-1.80)
≥30	8 (15.1)	367 (12.6)	1.04 (0.26-4.17)	1.16 (0.25-5.30)
Women				
<25	57 (42.9)	1748 (54.3)	1 [Reference][c]	1 [Reference][c]
25-29.99	42 (31.6)	1028 (31.9)	1.24 (0.75-2.05)	1.71 (1.01-2.91)
≥30	34 (25.6)	444 (13.8)	2.30 (1.39-3.81)	3.50 (2.00-6.14)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio.

[a] The number of study participants was divided by the total number (unknown and missing cases excluded) to calculate the percentage.

[b] The multivariate model is adjusted for age, history of cancer, ethnicity, and smoking status. In the subgroup analysis for women, we also adjusted for oral contraceptive use.

[c] Patients with a BMI less than 25 were the reference category.

Table 5. Stratification by Oral Contraceptive Use in Women

BMI	No. (%) of Study Participants[a]		Adjusted OR (95% CI)[b]
	Cases (n = 129)	Controls (n = 3148)	
No OC use			
<25	17 (13.2)	1190 (37.8)	1 [Reference][c]
25-29.99	11 (8.5)	843 (26.8)	0.85 (0.30-2.41)
≥30	7 (5.4)	384 (3.1)	1.29 (0.46-3.66)
OC use			
<25	36 (27.9)	486 (15.4)	5.09 (2.58-10.02)
25-29.99	31 (24.0)	186 (5.9)	11.87 (5.94-23.74)
≥30	27 (20.9)	59 (1.9)	29.26 (13.47-63.60)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); OC, oral contraceptive; OR, odds ratio.

[a] The number of study participants was divided by the total number (unknown and missing cases excluded) to calculate the percentage.

[b] The multivariate model is adjusted for age, history of cancer, ethnicity, and smoking status.

[c] Patients with a BMI less than 25 without OC use were the reference category.

women have higher plasma concentrations of prothrombotic factors, such as plasminogen activator inhibitor 1 and von Willebrand factor.[21] Obesity is also associated with increased activated protein C resistance and higher concentrations of factor VIII, which are risk factors for thrombosis.[22] Use of oral contraceptives also leads to increased activated protein C resistance,[23] which might explain the synergistic effect of both risk factors that we observed.

It is important to determine whether the control group we used is representative of the healthy population. In our study, the prevalence of a BMI of 30 or greater was 12.6% and 13.8% among male and female controls, respectively. These percentages are similar to the findings of a study[24] among healthy adults from the Netherlands that was performed in the same period as the MEGA study. The prevalence of a BMI above 25 among men and women is also comparable to the results of that study.

Of interest, obesity is also a risk factor for idiopathic intracranial hypertension (IIH). Patients with IIH most often present with headache, papilledema, and decreased visual acuity. Identical symptoms occur in intracranial hypertension owing to impaired venous return in patients with chronic CVT.[25] Before the introduction of computed tomography and magnetic resonance venography, it was not uncommon for patients with CVT to be misdiagnosed as having IIH.[26,27] Like CVT, IIH is far more common in women than in men, and the

association between IIH and obesity is also stronger in women than men.[28-30] Given these resemblances, it is intriguing to speculate on a possible common pathogenesis by which obesity increases the risk of both conditions in women. It has been hypothesized that IIH is caused by decreased outflow from the cerebral venous system, possibly owing to stenosis of the transverse sinuses or insufficiency of the valves in the jugular veins.[31,32] Studies[31,33] have suggested that obesity enhances this mechanism by transmittance of increased intra-abdominal pressure to the cerebral venous system. On the other hand, there are also data indicating that the sinus stenosis seen in IIH is secondary to the increased intracranial pressure and is reversible after removal of cerebrospinal fluid.[34] The effect of stenting of the cerebral sinuses has been examined in patients with IIH but only in small and uncontrolled series, and the data are inconclusive.[35,36] Prospective studies[37,38] evaluating the efficacy of cerebral venous sinus stenting in IIH are currently ongoing.

Our study has several limitations. First, we could include only a relatively small number of patients with CVT, especially men and women without oral contraceptive use. We cannot exclude that the absent association between obesity and CVT in these groups is the result of this limited sample size. Second, we were unable to examine whether genetic thrombophilia influences the association between obesity and CVT because screening for thrombophilia was not performed in most cases. Thrombophilia should be the focus of a future study given that there is a synergistic effect between oral contraceptives and thrombophilia on the risk of CVT[9,39] and between obesity and thrombophilia on the risk of VTE.[4] Third, data on the key variables of height and weight were missing in a substantial proportion of cases because these measurements were not recorded in all patients. This lack of data on height and weight could have underpowered the study and biased the results if the reason the data were missing was not random. To minimize this potential bias, we used a multiple imputation procedure.[16,40] The fact that 15.9% of cases in which no BMI could be calculated had obesity listed in their medical history also suggests that obesity was not infrequent among cases with missing BMI. Fourth, instead of measuring height and weight, we used self-reported data to calculate BMI, which could be less accurate, although a previous study[6] found an excellent correlation between self-reported and measured BMI. Moreover, because measurements were self-reported for cases and controls, any inaccuracy would be expected to affect both groups, which would decrease the risk of bias. Fifth, there was a time difference in recruitment between cases and controls. The controls were recruited from March 1, 1999, through September 31, 2004, whereas the cases were recruited from July 1, 2006 (Amsterdam), and October 1, 2009 (Berne), through December 31, 2014. A change in prevalence of obesity in that period could theoretically have biased the results. However, the time difference seems to be too small to explain the results and would also not explain why we only observed an association in women who used oral contraceptives. Finally, we cannot exclude the possibility that residual confounding influenced the results. Some variables, such as obstructive sleep apnea syndrome, were not available for controls. Obstructive sleep apnea syndrome is a risk factor for obesity and VTE, although, to our knowledge, an association with CVT has never been reported.[41,42]

The increased risk of VTE and CVT associated with oral contraceptives in the presence of obesity might make physicians reluctant to prescribe oral contraceptives to obese women. However, although the relative risks are increased substantially, the absolute risks of CVT are still small.[43] Moreover, withholding oral contraceptives may lead to an increase in unintended pregnancies and thus the number of pregnancy-related thrombosis cases.[44] Nevertheless, obese women should be informed about the increased risk of thrombosis if they use oral contraceptives, especially if other risk factors are present. Alternative methods of contraception that are not associated with thrombosis, such as an intrauterine device, might be offered to these women.

Conclusions

To our knowledge, this is the first case-control study that examined the association between obesity and CVT. Our results suggest that obesity is associated with a substantially increased risk of CVT in women who use oral contraceptives. This increased risk should be taken into consideration when prescribing oral contraceptives to obese women.

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REFERENCES

1. Brækkan SK, Hald EM, Mathiesen EB, et al. Competing risk of atherosclerotic risk factors for arterial and venous thrombosis in a general population: the Tromso study. *Arterioscler Thromb Vasc Biol*. 2012;32(2):487-491.

2. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors

and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002;162(10):1182-1189.

3. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. *Circulation*. 2010;121(17):1896-1903.

4. Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. *Br J Haematol*. 2007;139(2):289-296.

5. Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjønneland A, Overvad K. Anthropometry, body fat, and venous thromboembolism: a Danish follow-up study. *Circulation*. 2009;120(19):1850-1857.

6. Parkin L, Sweetland S, Balkwill A, Green J, Reeves G, Beral V; Million Women Study Collaborators. Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. *Circulation*. 2012;125(15):1897-1904.

7. Zuurbier SM, van den Berg R, Troost D, Majoie CB, Stam J, Coutinho JM. Hydrocephalus in cerebral venous thrombosis. *J Neurol*. 2015;262(4):931-937.

8. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med*. 2005;352(17):1791-1798.

9. de Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP; The Cerebral Venous Sinus Thrombosis Study Group. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in [correction of who are] carriers of hereditary prothrombotic conditions. *BMJ*. 1998;316(7131):589-592.

10. Koopman K, Uyttenboogaart M, Vroomen PC, van der Meer J, De Keyser J, Luijckx GJ. Risk factors for cerebral venous thrombosis and deep venous thrombosis in patients aged between 15 and 50 years. *Thromb Haemost*. 2009;102(4):620-622.

11. Zuurbier SM, Lauw MN, Coutinho JM, et al. Clinical course of cerebral venous thrombosis in adult acute lymphoblastic leukemia. *J Stroke Cerebrovasc Dis*. 2015;24(7):1679-1684.

12. Pearson V, Ruzas C, Krebs NF, Goldenberg NA, Manco-Johnson MJ, Bernard TJ. Overweight and obesity are increased in childhood-onset cerebrovascular disease. *J Child Neurol*. 2013;28(4):517-519.

13. deVeber G, Andrew M, Adams C, et al; Canadian Pediatric Ischemic Stroke Study Group. Cerebral sinovenous thrombosis in children. *N Engl J Med*. 2001;345(6):417-423.

14. Saposnik G, Barinagarrementeria F, Brown RD Jr, et al; American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(4):1158-1192.

15. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722.

16. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087-1091.

17. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. *Thromb Haemost*. 2003;89(3):493-498.

18. Kemmeren JM, Tanis BC, van den Bosch MA, et al. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke*. 2002;33(5):1202-1208.

19. Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. *JAMA*. 1997;277(8):642-645.

20. Bonita R, Beaglehole R, Kjellstrom T. *Environmental and Occupational Epidemiology: Basic Epidemiology*. 2nd ed. Geneva, Switzerland: World Health Organization; 2006:93-95.

21. De Pergola G, De Mitrio V, Giorgino F, et al. Increase in both pro-thrombotic and anti-thrombotic factors in obese premenopausal women: relationship with body fat distribution. *Int J Obes Relat Metab Disord*. 1997;21(7):527-535.

22. Christiansen SC, Lijfering WM, Naess IA, et al. The relationship between body mass index, activated protein C resistance and risk of venous thrombosis. *J Thromb Haemost*. 2012;10(9):1761-1767.

23. Rosing J, Middeldorp S, Curvers J, et al. Low-dose oral contraceptives and acquired resistance to activated protein C: a randomised cross-over study. *Lancet*. 1999;354(9195):2036-2040.

24. Schokker DF, Visscher TL, Nooyens AC, van Baak MA, Seidell JC. Prevalence of overweight and obesity in the Netherlands. *Obes Rev*. 2007;8(2):101-108.

25. Wall M, Kupersmith MJ, Kieburtz KD, et al; NORDIC Idiopathic Intracranial Hypertension Study Group. The Idiopathic Intracranial Hypertension Treatment Trial: clinical profile at baseline. *JAMA Neurol*. 2014;71(6):693-701.

26. Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. *Neurology*. 1999;53(7):1537-1542.

27. Leker RR, Steiner I. Features of dural sinus thrombosis simulating pseudotumor cerebri. *Eur J Neurol*. 1999;6(5):601-604.

28. Kesler A, Goldhammer Y, Gadoth N. Do men with pseudomotor cerebri share the same characteristics as women? a retrospective review of 141 cases. *J Neuroophthalmol*. 2001;21(1):15-17.

29. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664-670.

30. Balcer LJ, Liu GT, Forman S, et al. Idiopathic intracranial hypertension: relation of age and obesity in children. *Neurology*. 1999;52(4):870-872.

31. Nedelmann M, Kaps M, Mueller-Forell W. Venous obstruction and jugular valve insufficiency in idiopathic intracranial hypertension. *J Neurol*. 2009;256(6):964-969.

32. Wakerley BR, Tan MH, Ting EY. Idiopathic intracranial hypertension. *Cephalalgia*. 2015;35(3):248-261.

33. Sugerman HJ, DeMaria EJ, Felton WL III, Nakatsuka M, Sismanis A. Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri. *Neurology*. 1997;49(2):507-511.

34. Rohr A, Dörner L, Stingele R, Buhl R, Alfke K, Jansen O. Reversibility of venous sinus obstruction in idiopathic intracranial hypertension. *AJNR Am J Neuroradiol*. 2007;28(4):656-659.

35. Puffer RC, Mustafa W, Lanzino G. Venous sinus stenting for idiopathic intracranial hypertension: a review of the literature. *J Neurointerv Surg*. 2013;5(5):483-486.

36. Piper RJ, Kalyvas AV, Young AM, Hughes MA, Jamjoom AA, Fouyas IP. Interventions for idiopathic intracranial hypertension. *Cochrane Database Syst Rev*. 2015;8:CD003434.

37. ClinicalTrials.gov. Venous Sinus Stenting for Idiopathic Intracranial Hypertension Refractory to Medical Therapy (VSSIIH). NCT01407809. https://clinicaltrials.gov/ct2/show/NCT01407809. Accessed December 1, 2015.

38. ClinicalTrials.gov. Stenting of Venous Sinus Stenosis for Medically Refractory Idiopathic Intracranial Hypertension. NCT02143258. https://clinicaltrials.gov/ct2/show/NCT02143258. Accessed December 1, 2015.

39. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. *N Engl J Med*. 1998;338(25):1793-1797.

40. Moons KG, Donders RA, Stijnen T, Harrell FE Jr. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol*. 2006;59(10):1092-1101.

41. Chou KT, Huang CC, Chen YM, et al. Sleep apnea and risk of deep vein thrombosis: a non-randomized, pair-matched cohort study. *Am J Med*. 2012;125(4):374-380.

42. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet*. 2014;383(9918):736-747.

43. Middeldorp S. Thrombosis in women: what are the knowledge gaps in 2013? *J Thromb Haemost*. 2013;11(suppl 1):180-191.

44. van Vlijmen EF, Veeger NJ, Middeldorp S, et al. Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception. *Blood*. 2011;118(8):2055-2061.